JOEM • Volume 42, Number 8, August 2000

Ammonium Perchlorate Contamination of Colorado River Drinking Water is Associated With Abnormal Thyroid Function in Newborns in Arizona

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The Colorado River below Lake Mead, which supplies drinking water for approximately 20,000,000 people, is contaminated by ammonium perchlorate. We identified populations who were exposed and unexposed to perchlorate-contaminated drinking water and compared median newborn thyroid-stimulating hormone (TSH) levels after adjusting for age in days at measurement and for race/ethnicity. Median newborn TSH levels in a city whose drinking water supply was 100% perchlorate-contaminated water from the Colorado River below Lake Mead were significantly higher than those in a city totally supplied with non–perchlorate-contaminated drinking water, even after adjusting for factors known or suspected to elevate newborn TSH levels. This ecological study demonstrates a statistically significant association between perchlorate exposure and newborn TSH levels. It suggests that even low-level perchlorate contamination of drinking water may be associated with adverse health effects in neonates and highlights the need for both further study and control of human low-level perchlorate exposure. (J Occup Environ Med. *2000;42:777–782*)

For over 50 years, ammonium perchlorate (AP) has been used as an oxidizer in solid propellants for rockets, missiles, fireworks, and munitions; for manufacture of matches; and in analytical chemistry. Because of its short shelf life, it is necessary to periodically replace AP in the nation's missile and rocket inventory. Millions of pounds of AP are produced annually in the United States, and large quantities of the compound have been disposed of in Nevada since the 1950s.[1–3] Facilities in Henderson, Nevada, that manufacture AP for the Department of Defense and the National Aeronautical and Space Administration have been sources of contamination by perchlorate[2] and have at least one large plume containing perchlorate in contact with the Las Vegas Wash, a tributary feeding Lake Mead and the Colorado River.[4]

The perchlorate ion is formed when AP dissociates. Under arid conditions perchlorate can precipitate with cations, resulting in a long-term source for redissolution.[5,6] Perchlorate is extremely soluble and exhibits low volatility in water. It is quite resistant to treatment with powder-activated carbon and is not removed from water by conventional water treatment facilities. These factors can cause it to persist for very long periods in water. AP containment is a major issue for Las Vegas and other areas that receive drinking water from the Colorado River be-

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low Lake Mead. Approximately 20,000,000 persons in Arizona, California, and Nevada drink water from this source.[2]

The reference-dose for humans for perchlorate, defined as the daily oral exposure to humans likely to be without risk of deleterious health effects during a lifetime, has not been determined with certainty. Until March 1997, levels of perchlorate had to be at least 400 ppb or μg/liter to be detected. In March 1997, ion chromatography was used to detect levels as low as 1 to 4 ppb. In 1997, the California Department of Health Services introduced an interim action level of 18 ppb for perchlorate in drinking water. Perchlorate levels above 1000 ppb have been detected in the Las Vegas Wash, and levels up to 16 ppb have been measured in the raw water intake for Las Vegas. Perchlorate has also been detected in water along the Colorado River[2] and in influent and effluent water taken from the Central Arizona Project water treatment plants.[7] In contrast, perchlorate has not been detected in Salt River Project water, a source independent of the Colorado River.

Perchlorate affects thyroid function in humans by acting as a competitive inhibitor of iodide transport in the thyroid.[8-10] Unlike iodide, perchlorate does not undergo metabolic transformation in the gland. When iodine intake is normal or low, perchlorate can inhibit iodide accumulation sufficiently to cause goiter and hypothyroidism. When iodine intake is high, however, sufficient iodide can enter the gland to permit normal rates of hormone synthesis. Because perchlorate crosses the placenta,[11] it has the potential to cause hypothyroidism in the fetus and in newborns. Some potentially harmful effects of hypothyroidism on developing fetuses are abnormal cognitive function; abnormal gait; impaired fine motor skills; and abnormal vision, hearing, and speech.

This study addresses the possible impact of perchlorate-contaminated drinking water from the Colorado River on newborn thyroid function. Specifically, we sought to determine whether there is an association between maternal exposure to Colorado River drinking water and neonatal thyroid function.

Methods

Water Supply and Perchlorate Exposure

We contacted water supply agencies in cities in Arizona with populations over 50,000 to determine what percentage of their drinking water came from the Colorado River below Lake Mead. The only area identified that had essentially all of its drinking water supplied by the Colorado River below Lake Mead was Yuma (zip codes 85364–6 and 85369, population 68,000). The only area identified that had none of its drinking water supplied by the Colorado River below Lake Mead was Flagstaff (zip codes 86001–4 and 86011, population 58,000). Water treatment plants in both Yuma and Flagstaff are conventional water treatment plants. Attempts to determine the percentage of drinking water from the Colorado River by zip code in other cities were unsuccessful. Most areas had mixed sources of water (Colorado River, Salt River, Central Arizona Project, ground water, and local lakes, to name a few). Therefore, only Yuma and Flagstaff were studied. Recently, measurements of perchlorate levels in the drinking water supplies of Yuma and of Flagstaff were performed by the United States Environmental Protection Agency (USEPA)[12] (and personal communication, Kevin Mayer, SFD-7–2, Superfund Site Cleanup Branch, USEPA Region 9, October 6, 1999) and the Arizona Department of Environmental Quality (personal communication, Dale Ohnmeiss, Manager, Drinking Water Section, Arizona Department of Environmental Quality, September 2, 1999).

Newborn Thyroid Function

Newborn thyroid function was assessed by using data from the Arizona Newborn Screening Program (NBS). The NBS is a statewide program designed to identify at birth babies who have some type of serious medical condition. In Arizona, newborns are screened for congenital hypothyroidism as well as phenylketonuria, biotinidase deficiency, maple syrup urine disease, galactosemia, hemoglobinopathies, and homocystinuria. Newborn screening program data in Arizona have been computerized since late 1994. Laboratory specimens are sent to the State of Arizona Department of Health Services Laboratories. Specimens received on any given day are placed in batches, and the total thyroxine (T4) is assayed in each sample. The laboratory uses a standard software package (Neometrics MSDS III, Neometrics, Inc, East Northport, NY) to select approximately 10% of the samples from each batch with the lowest T4 levels; a TSH is measured on each of the selected samples. T4 is measured by time-resolved radioimmunoassay using NeoCoat T4 kits (Neometrics), and TSH is measured by using ACCUSCREEN TSH (Neometrics Inc). The T4 levels and the corresponding TSH levels for the 10% of samples with the lowest T4 levels are entered into the computerized NBS database; the remaining values are not.

Subjects

There were 365,541 records belonging to 274,971 unique newborns entered into the computerized Arizona NBS database between October 1994 and the end of 1997 (Fig. 1). If more than one TSH value was recorded for the same newborn, only the record with the first TSH level was retained. There were 35,668 records of unique newborns with their first TSH levels. Of these, there were 1081 records with missing zip codes and/or addresses. By using

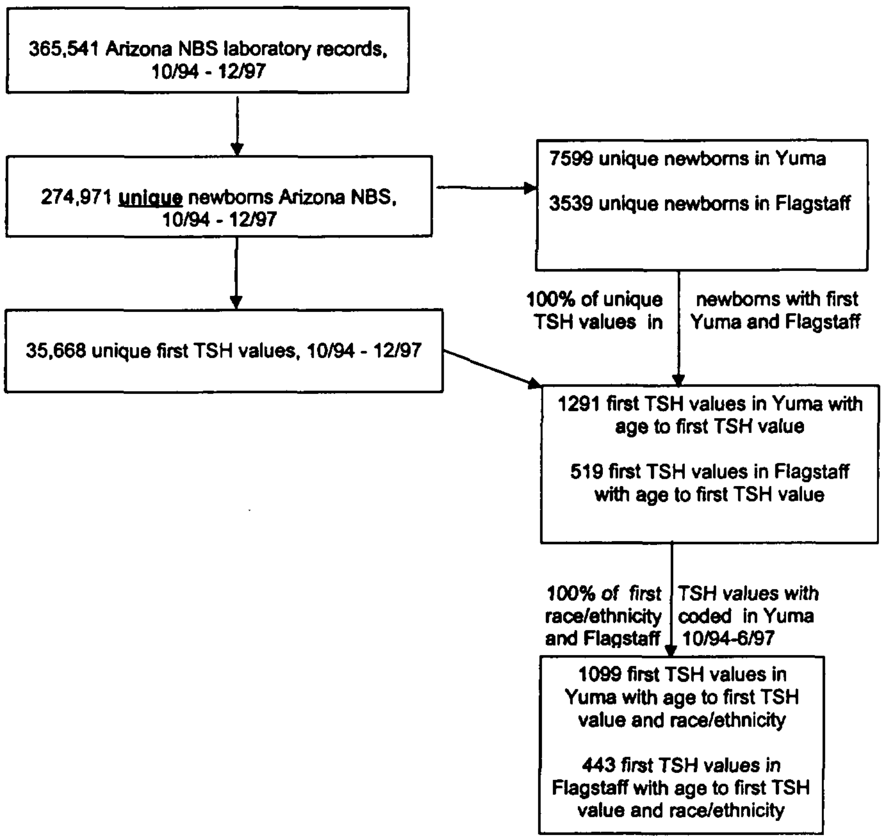

Fig. 1. Arizona Newborn Screening Program (NBS) flow chart of data. TSH, thyroid-stimulating hormone.

Geographic Information System software and hand searches, we were able to identify and enter zip codes for 596 of these. After adding these zip codes, there were 1291 first TSH levels in Yuma that had values for age in days at time of first TSH measure, and there were 519 first TSH levels in Flagstaff that had values for age in days at time of first TSH. There were 1099 first TSH levels in Yuma with race/ethnicity recorded that had values for age in days at time of first TSH, and there were 443 first TSH levels in Flagstaff with race/ethnicity recorded that had values for age in days at time of first TSH. The range of age in days at time to first TSH was 0 to 132 in Yuma and 0 to 109 in Flagstaff; the longer times are likely to belong to babies who were born elsewhere and then brought into the catchment area.

Statistical Analysis

Data were analyzed by using the Statistical Package for the Social Sciences version 9.0 (SPSS Inc, Chicago, IL). TSH levels are highest at birth and decline over the next few days.[13] Therefore we decided to stratify on age in days from birth to first TSH value. Because some studies have reported that race/ethnicity may affect newborn TSH levels,[14] we stratified by race/ethnicity and compared median TSH levels in Yuma and Flagstaff by using the Mann-Whitney non-parametric two-sample test. Because the distribution of the TSH values is very skewed, analysis of variance applied to $\log_e(\mathrm{TSH}+1)$ was used to assess whether city of birth (and, thus, drinking water source) was associated with newborn TSH levels after adjusting for age in days since birth to first TSH level (categorized as 0 [ie, <1]; 1,2,3,4; or 5+ days) and race/ethnicity (Hispanic or non-Hispanic). We used $P < 0.05$ to determine statistical significance.

Results

Between October 24, 1994 and December 27, 1997, the Arizona NBS recorded 7599 unique newborns in Yuma and 3539 in Flagstaff (Fig. 1). Of these, there were 1099 unique newborns in Yuma and 443 in Flagstaff with first TSH levels and race/ethnicity coded (Fig. 1). The median first TSH level (Table 1) in Yuma (19.9 mU/liter, interquartile range 12.5 to 28.3) was significantly higher than the median level in Flagstaff (13.4, 8.8 to 18.9, $P <$ 0.000001). The differences occurred in both non-Hispanics and Hispanics (Table 1).

To compare TSH levels between Yuma and Flagstaff while controlling for age in days since birth and race/ethnicity, we computed effect sizes and t tests for $\ln(\mathrm{TSH}+1)$ between Yuma and Flagstaff for each day separately for non-Hispanics and Hispanics (Table 2). Although the individual t tests were not significant, the direction of the effect (Yuma higher than Flagstaff) was mostly consistent.

To provide an overall test of significance comparing Yuma and Flagstaff, adjusting for age in days since birth and race/ethnicity, we performed an analysis of variance on the log-transformed TSH values. The mean level of TSH for newborns in Yuma was significantly higher than in Flagstaff (P = 0.017). Race/ethnicity was not a significant factor in the model (P = 0.47). As expected, the effect of age in days to TSH measurement was highly significant ($P < 0.001$).

The criteria for evaluating TSH in both cities were the same (ie, the central laboratory used a common cut point for the T4 values in both cities). A higher percent of T4 values met the criteria for being sent for a TSH value in Yuma than in Flagstaff

TABLE 1
Median TSH Levels (mU/liter) by City and Race/Ethnicity*

	Yuma			Flagstaff			
	n	Median	Interquartile Range	*n*	Median	Interquartile Range	*P* Value
All with race recorded	1,099	19.9	12.5–28.3	443	13.4	8.8–18.9	<0.000001
Non-Hispanic	447	19.3	11.9–28.8	385	13.6	8.8–18.8	<0.000001
Hispanic	652	20.2	12.8–28.0	58	12.3	8.7–19.8	=0.000005

* TSH, thyroid-stimulating hormone.

TABLE 2
TSH Levels (mU/liter) by City of Birth, Age in Days, and Race/Ethnicity*

		Observed TSH Values						Tests Based on ln(TSH + 1)	
	Days to TSH	Median	Mean	SD	SEM	Frequency	% Newborns With TSH	*t* test Yuma vs Flagstaff	Effect Size
Flagstaff									
Non-Hispanic	0	23.27	23.17	12.71	3.53	13	22.3	−1.47	−0.57
	1	22.23	23.01	7.80	0.78	101	11.3	−0.69	−0.07
	2	13.38	13.29	5.57	1.19	22	10.4	−2.22	−0.51
	3	11.60	17.90	35.35	7.37	23	16.4	0.27	0.10
	4	12.70	11.34	4.70	1.30	13	19.7	−1.41	−0.62
	5	10.62	10.78	5.56	0.38	213	18.3	−0.51	−0.06
	Total	13.56	14.99	11.92	0.61	385	15.2	−5.83	−0.41
Hispanic	0	33.06	33.06			1	8.3		
	1	20.84	24.10	19.17	4.18	21	12.1	−0.88	−0.24
	2	13.60	16.57	12.03	6.94	3	8.6	−0.23	−0.19
	3	10.15	10.15			1	10.0		
	4	10.04	10.04	3.59	2.54	2	25.0	0.60	0.23
	5	10.82	9.95	5.18	0.95	30	17.0	−1.39	−0.35
	Total	12.26	15.82	14.08	1.85	58	14.0	−2.99	−0.46
Yuma									
Non-Hispanic	0	30.50	32.38	14.61	2.34	39	24.5		
	1	26.06	32.66	70.29	4.84	211	18.0		
	2	16.11	17.79	10.79	1.44	56	12.3		
	3	11.98	11.51	5.46	1.73	10	17.5		
	4	13.93	14.82	5.36	2.40	5	18.5		
	5	11.01	11.21	5.82	0.52	126	15.1		
	Total	19.33	24.05	49.56	2.35	447	16.5		
Hispanic	0	30.32	30.42	15.68	1.73	82	37.4		
	1	24.67	25.70	11.43	0.64	320	18.5		
	2	16.85	16.99	6.48	0.84	60	11.3		
	3	15.54	15.38	4.40	1.33	11	18.3		
	4	11.59	10.84	7.16	2.07	12	40.0		
	5	11.75	11.81	5.79	0.45	167	14.9		
	Total	20.21	21.49	12.47	0.49	652	17.6		

* TSH, thyroid-stimulating hormone; SD, standard deviation; SEM, standard error of the mean.

(Table 1). This is consistent with the result that the TSH levels in Yuma are higher than those in Flagstaff.

We reviewed the available data to document perchlorate levels in the drinking water supplies of Yuma and Flagstaff. Data were not available between 1994 and 1997, particularly because the tests for perchlorate in water were not very sensitive until later in 1997. In August 1999, perchlorate levels in Yuma were 6 ppb and were the same in both raw water and finished drinking water.[12] In Flagstaff, in September 1999, perchlorate levels in both raw and finished drinking water were undetectable in testing by the USEPA Region 9 Laboratory (personal communication, Kevin Mayer, Superfund Site Cleanup Branch, October 6, 1999). Selenium was not detectable in the water supply of either city. Because the water processing facilities have not changed, and perchlorate is known to persist for very long periods in water, these recent readings strongly suggest that differences in perchlorate levels existed during the study period.

Discussion

We compared newborns in Yuma, a city that obtains its public drinking water entirely from the Colorado River below Lake Mead, with newborns in Flagstaff, a city that obtains none of its public drinking water from the Colorado River below Lake Mead. We found that median newborn TSH levels in Yuma were significantly higher than in Flagstaff. This remained true after adjusting for factors known or suspected to affect newborn TSH levels, including age in days at measurement of the first TSH level and race/ethnicity. These results demonstrate an association between city of birth, water source, maternal perchlorate exposure, and TSH levels in newborns. Newborns of exposed mothers had significantly higher TSH levels than newborns of non-exposed mothers, which suggested that even low-level perchlorate contamination of drinking water may be associated with adverse health effects in neonates.

There are some limitations to this study. This was an ecological study. We did not sample tap water in homes across the state or directly measure individual exposure to perchlorate. Available data do, however, indicate that the public water supply in Yuma is contaminated with perchlorate and that the supply in Flagstaff is not. We do not have information on drinking water iodine levels from either city. In general, the iodine content of drinking water is too low to be recognized as a source of iodine, and there is no prior reason to suspect that dietary iodine intake would differ between Yuma and Flagstaff. The study was limited to two cities. This was because we were unable to localize the percentage of drinking water from specific water sources to zip codes across most of the state of Arizona. The cities were, however, comparable in size and socioeconomic status (Yuma population: 68,000, with 84% above the federal poverty level; Flagstaff population: 58,000, with 83% above the federal poverty level). We were limited in our analyses to variables already in the NBS data set. For example, we did not know gestational age at birth or birth weight for many of the infants. Fortunately, although very low birth weight infants (< 1500 g) have lower T4 levels than term infants, they also seem to have attenuated TSH surges and mean TSH levels no higher than term infants.[15] Thus, it is unlikely that potential differences in gestational age or birth weight biased our results. Finally, we do not know what adverse health impact, if any, was associated with this extent of change in neonatal TSH levels. Most studies have demonstrated that neonatal hypothyroidism that is rapidly diagnosed and appropriately treated is associated with normal childhood intelligence.[16–18] Nevertheless, some studies have demonstrated subtle residual deficits in cognitive function, language, hearing, and vestibular function,[19,20] especially in those with prenatal onset of hypothyroidism.[21] It is likely that hypothyroidism associated with perchlorate exposure is transient. Nevertheless, it does not seem prudent to assume that the observed changes in neonatal thyroid function are harmless.

Other recent studies suggest that there are no untoward effects of AP exposure on thyroid function in humans.[2,10,22] It is important to note that Gibbs et al were studying airborne exposure to AP, not exposure from drinking water. With respect to the recent reports of Lamm and Doemland,[2] it is important to note that their outcome of interest was either congenital hypothyroidism or T4 values. We investigated the effect of perchlorate on a much more sensitive measure of newborn thyroid function, the TSH value.[23] It is interesting to note that during the period from October 1994 through August 1999, the Arizona NBS reported four cases of congenital hypothyroidism in Yuma and none in Flagstaff (personal communication, Ruthann Smejkal, PhD, Chief, Newborn Screening Program, Arizona Department of Health Services, September 1, 1999). This was not statistically significant. Also of interest is the fact that neonatal T4 values did not differ between Yuma and Flagstaff after adjusting for race/ethnicity (data not shown).

Our data demonstrate an association between low-level perchlorate exposure and newborn TSH levels and suggest that the effects of AP-contaminated drinking water on humans requires further study, including systematic measurements of exposure and outcomes. In addition, appropriate interventions to limit human exposure to perchlorate should be undertaken.

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